Remarks:

Applicants acknowledge, with thanks, the courtesy shown their undersigned representatives, by Examiner Shirley Gembeh and Supervisory Examiner Ardin Marschel during the telephone interview of December 13, 2006. While no agreement was reached in that interview regarding the patentability of the pending claims, a number of useful amendments were discussed and those deemed to possibly overcome the pending rejections are incorporated herein.

Applicants also respectfully request entry of the amendment to their specification submitted herewith. The paragraph to be inserted is excerpted from the specification of Applicants' co-pending application 10/629,308 which has been incorporated by reference into the pending application and therefore does not represent new matter.

1. Summary of Pending Rejections:

As currently amended, claims 1, 11-12, 20, 23-37, 39-64 and 71-78 are pending. Claims 13-19, 21, 23, 65 and 70 have been cancelled. The Office Action of October 19, 2006 ("the Office Action") rejected all of the pending claims.

Claims 1, 11-12, 20, 23-37, and 49-64 have been rejected based upon the written description requirement of 35 U.S.C. § 112, first paragraph for allegedly failing to reasonably convey that Applicants were in possession of the claimed invention. (Rejection alleges inadequate disclosure of a representative number of claimed compounds.)

Claims 1, 11-12, 20-37, and 39-48 also have been rejected based upon the written description requirement of 35 U.S.C. § 112, first paragraph for allegedly containing new subject matter. (Rejection alleges no basis for "w/v" in claims.)

Further, claims 11-12, 23-26, 40-48, 50-55, 63-64, 66, 72, and 76 have been rejected under 35 U.S.C. § 112, second paragraph for purported indefiniteness. (Rejection refers to multiple uses of "about.")

Claims 51-57 have been rejected for alleged lack of antecedent basis. (No antecedent recitation of "Poloxamer 188.")

Claim 78 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to set forth the subject matter Applicants regard as their invention. (Rejection questions whether a composition can be clear and yet have "particle sizes.")

Under 35 U.S.C. § 103, claims 49-64, 66-68, and 71-74 have been rejected unpatentable over U.S. 4,056,635 to Glen et al. ("Glen") taken with WO 03/17977 A1 to Meadow et al. ("Meadow") in view of U.S. 6,140,374 to May et al. ("May") and U.S. 6,743,436 to Lee et al. ("Lee"). Finally, claims 75-77 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Glen in view of Meadow and further in view of May and Lee.

2. Summary of amendments herein, as discussed in the December 15, 2006 telephone interview:

a. The term "(w/v)" has been removed from the pending claims. All compositions are recited as weight per volume (gram/100 ml) percentages and the claims have been amended to so indicate. Support is found in the specification at page 33, line 17 to page 34 line 1. Applicants respectfully submit that this addresses the rejection under *35 U.S.C. § 112, ¶ 1 (New Matter) of claims 1, 11-12, 20-37, and 39-48*

b. Usage of the term "about" at various claims has been modified to avoid use of two "about" terms in relation to the same limitation. Applicants respectfully submit that this addresses the rejection under 35 U.S.C. § 112, ¶ 2 (Indefiniteness) of claims 11-12, 23-26, 40-48, 50-55, 63-64, 66, 72 and 78.

c. Claim 49 has been amended to rectifythe lack of antecedent basis for "poloxamer 188" in claims 51-57.

d. The transition phrase "comprising" has been replaced with "consisting essentially of" in several of the claims where appropriate. Applicants' additional remarks, below, compare their invention as recited in their amended claims to the cited prior art.

3. Response to remaining rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103 rejections.

A. 35 U.S.C. § 112, ¶ 1 (Possession of Invention): Claims 1, 11-12, 20-37, and 39-48

The Office Action rejects claims 1, 11-12, 20, 23-37, and 49-64 based upon the written description requirement of 35 U.S.C. § 112, first paragraph for allegedly failing to reasonably convey that Applicants were in possession of the claimed invention at the time the application was filed. The Office Action states that Claim 1 recites one or more pH modifiers, stabilizers or tonicity modifiers but does not describe or exemplify them.

Applicants respectfully traverse this rejection because Applicants have described and exemplified each of the claimed features of claim 1. Specifically, Applicants explicitly define pH modifiers in the specification (all references to "the specification" are to Applicants' specification as originally filed) at page 24, beginning on line 4:

> *The term "pH modifier," as used herein, refers to substances such as acids, bases, or salts thereof that are used to adjust the pH of a composition and that are well known to those of skill in the art.*

Moreover, Applicants specifically identify exemplary acids and bases in the immediately preceding text beginning on page 23, line 31:

> *The pH of the propofol containing compositions can be adjusted as necessary by, for example, the addition of a base or a salt thereof, for example, an alkali such as sodium hydroxide, potassium hydroxide, or the like. Alternatively, an acid or a salt thereof such as hydrochloric acid, citric acid, or the like can be used to adjust the pH of the compositions.*

With respect to "stabilizers," Applicants identify an exemplary stabilizer as citric acid in at page 17, beginning on line 18:

> *In addition, preferred formulations of the invention can also comprise citric acid or a salt thereof. Without being held to any particular theory, Applicants believe that citric acid or a salt thereof in the compositions of the present invention exhibits antioxidant and/or chelating properties.* ***Applicants have discovered that compositions comprising citric acid or a salt thereof possess an unexpectedly high degree of propofol stability.*** *(emphasis added)*

Additional support for the term "stabilizers" can be found in the amendment to the specification submitted herewith whereby Applicants disclose that antioxidants and chelating agents are exemplary stabilizers and citric acid, cysteine, and EDTA are more specific examples:

> (1) water, 2,6-diisopropylphenol, poloxamer 188, polyethylene glycol 400, propylene glycol, optionally, a tonicity modifier, and, optionally, a pH modifier, **or stabilizer (e.g., antioxidant such as cysteine, chelating agent such as EDTA, or other such as citric acid).** (emphasis added)

With respect to "tonicity modifiers," Applicants identify several exemplary compounds at page 16, beginning on line 4:

> *The compositions may additionally comprise one or more tonicity modifiers. Examples of tonicity modifiers include, but are not limited to, lactose, dextrose, dextrose anhydrous, mannitol, sodium chloride, potassium chloride, propylene glycol and glycerol.*

Applicants have directed the Examiner to the portions of their specification that provide disclosure sufficient to support the claimed features identified by the Office Action within the meaning of § 112, ¶ 1. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. 35 U.S.C. § 112, ¶ 2 (clear to the eye): Claim 78

In numbered paragraph V, the Office Action rejects claim 78 under 35 U.S.C. § 112, second paragraph for alleged failure to set forth the subject matter Applicants regard as their invention based on Applicants' average particle size claim limitation of "about 30 to about 75 nanometers," in combination with the claim limitation, "clear to the naked eye."

Applicants respectfully traverse this rejection. Applicants' invention as claimed is a clear aqueous formulation. Indeed, this characteristic is a surprising feature of the invention as claimed – **Applicants respectfully submit that the Office Action's expression of skepticism that their formulation is clear is itself indicative of these surprising results.** Nevertheless, Applicants' specification discloses several exemplary data points within the range of the claimed particle size of "about 30 to about 75 nanometers" that nevertheless produce a formulation that is "clear to the naked eye." Table II, excerpted below from Applicants' specification at page 35, illustrates the data:

TABLE II: PHYSICAL PROPERTIES OF EXEMPLARY PROPOFOL FORMULATIONS

Formulation Identity:	Avg. Particle Size (nm)	Polydispersity Index	Osmolality (mmol/kg)	Appearance	Physical Stability* (days)
M841	56	0.21	299	Clear	14
M831	55	0.22	292	Clear	14
M840	50	0.23	175	Clear	14
M830	57	0.21	162	Clear	14
M741	51	0.19	302	Clear	14
M740	47	0.17	295	Clear	14
M731	50	0.19	255	-	-
M730	49	0.18	153	-	-
M641	-	-	-	Hazy	X†
M642	50	0.15	400	Hazy	X†
M661	54	0.16	370	Less Hazy	X†
M660	-	-	-	Less Hazy	X†
M920	50	0.21		Clear	13

* Time during which no change in particle size is detected.
† "X" indicates that the sample is not a clear solution after fourteen days, and is not considered physically stable.

Empirical data notwithstanding, and without being bound to theory, Applicants believe the phenomenon of the formulation being "clear to the naked eye" is because the particles reported in Applicants' Table II are nano-sized droplets comprised chiefly of surfactant (e.g. poloxamer) distributed through the aqueous medium and because the droplets have a refractive index close to water. Since these droplets are smaller than the wavelength of visible light (400-700nm) and have a refractive index similar to the aqueous medium, they do not scatter much light and appear clear when viewed.

In light of Applicants' exemplary empirical data and the explanation thereof it is respectfully requested that this rejection be withdrawn.

C. 35 U.S.C. § 103(a) Rejection: (Glen and Meadow in view of May and Lee): Claims 49-64, 66-68, and 71-74.

The Office Action rejected claims 49-64, 66-68, and 71-74 under § 103(a) based on Glen and Meadow in view of May and Lee.

The Office Action began by alleging that Glen teaches Applicants' claim 1. To this end, the Office Action cited to various portions of Glen that generally disclose 2,6-diisopropylphenol, water, a block copolymer, and citric acid. The Office Action went on to cite Glen's Example 9 as

disclosing a clear solution. Applicants respectfully submit that their invention as claimed in claim 1 is distinguishable from the composition disclosed in Example 9 of Glen on at least two grounds. First, the composition that Example 9 of Glen discloses as "clear" is not aqueous as recited in Applicants' claim 1 (see Glen, col. 5, lines 60-68) because Example 9 of Glen teaches 'Cremophor' RH40 as a surfactant. Glen itself recognizes Cremophor RH40 is a castor oil derivative (Glen, col. 1, lines 63-66) which is a lipid component that precludes describing Example 9 as an aqueous composition. Second, those compositions of Glen's Example 9 that do not disclose Cremophor as a component (i.e. examples 'h" and "i" which instead disclose Tween as a surfactant) teach formulations whose total excipient concentration exceeds Applicants' recited limitation of "up to 15%" – example "h" discloses 20% excipients and example "i" discloses 23% excipients. Accordingly, Glen fails to teach or suggest a propofol composition that is clear, aqueous, and the excipient concentration of which does not exceed 15%.

The Office Action next addresses Applicants' claims 49-57 by apparently citing to Glen col. 3, lines 27-28. This portion of Glen generally discloses that "from 10-20% by weight... of a polyoxyethylene-polyoxypropylene block copolymer, especially 'Pluronic' F68 can be used in propofol compositions and asserting that it "will be obvious to one of ordinary skill to modify to achieve the instantly claimed invention." Applicants respectfully submit that claim 49, as amended, is distinguishable from Glen in that Glen fails to teach or suggest an aqueous propofol composition that is clear and consists essentially of excipients that constitute up to 15% of the total formulation.

The Office Action next purports to address Applicants' claim 13 "where the block copolymer -is a Poloxamer 188," however, Applicants claim 13 was cancelled by Applicants' Amendment of June 29, 2006. Accordingly, Applicants respectfully submit that this rejection is moot. A similar error appears to have occurred where the Office Action in the following paragraph (first paragraph, page 7) purports to address claims 16 (also cancelled by Amendment of June 29, 2006), 20 (amended to depend from claim 1 by Amendment of June 29, 2006) and 19 (also cancelled by Amendment of June 29, 2006). Applicants respectfully submit that hese rejections are likewise moot.

The Office Action next addresses claims 49-57 at page 7, paragraph 2 by citing to Glen col. 6, lines 7-8 as teaching Applicants' PEG limitation. Applicants respectfully submit that this passage of Glen is distinguishable because it discloses **propylene** glycol (not **polyethylene** glycol as Applicants claim) and does so in the context of a lipid-based formulation comprising 'Cremophor' EL. Likewise, the next sentence of the Office Action cites col. 9, line 7-8 of Glen for the use of citric acid, and Applicants respectfully submit that this portion of Glen is also

distinguishable because it is in the context of a lipid-based formulation containing 'Cremophor' RH40.

The next sentence of the Office Action at page 7, paragraph 2 cites to Glen at col. 1, lines 5-7 for administration to induce anesthesia as teaching Applicants' claim 73. However, Applicants' claim 73 recites "[a] method of inducing or maintaining anesthesia in a mammal comprising administering to said mammal an amount of a formulation, as claimed in any one of claims 1, 49, 75, or 66, effective to induce or maintain anesthesia." While Applicants' appreciate (and acknowledge as part of their own Background of the Invention disclosure) that 2,6-diisopropylphenol is recognized in the art as an anesthetic, Applicants respectfully submit that Glen does not teach or suggest their inventive compositions as claimed in claims 1, 49, 75, or 66, for the reasons discussed above.

The next sentence of the Office Action page 7, paragraph 2 generally asserts that Applicants' "[c]laim 74 is obvious, as the formulation will comprise a container because in other [sic, order] to dispense the formulation would have to be in a container." Applicants respectfully submit that an inventive feature of the invention as claimed in claim 74 is that the container is a "multi-use container." This advantageous feature is enabled by Applicants' inventive formulation that is sufficiently resistant to microbial growth to permit repeated withdrawal from a single container. See, e.g., Applicants' specification at page 27, line 27 to page 28, line 9.

The Office Action proceeds, in several of its subsequent citations, to invoke Lee - particularly Examples 5-11 disclosed by Lee at column 6-8. Applicants respectfully submit that Lee is distinguishable from their invention as claimed on several bases. For example, each of the Examples disclosed by Lee, with the exception of Example 7, make extensive use of Poloxamer 407 and/or lipid-based surfactants such as SOLUTOL HS while Applicants' claims as amended are directed to Poloxamer 188 and aqueous formulations. Example 7 is further characterized by the use of 5% ethanol and a total excipient concentration of 18%. These various features of the Examples of Lee preclude their teaching or suggestion of the Applicants' invention as claimed in claim 49 due to the limit of 15% on total excipients and the "no other glycol or alcohol" limitation.

The Office Action proceeds at page 7, third paragraph to address claims 49, 66, and 72 by citing to columns 7 and 8 of Lee for a teaching that the block copolymer is less than 10% of the composition. First, with respect to claim 72, as noted previously, Applicants respectfully submit that columns 7 and 8 of Lee each teach Poloxamer 407 in every example except for Example 7 at col. 7, lines 31-44. Applicants' claim 72, in contrast, recites "[a]n aqueous

formulation consisting essentially of: a) a block copolymer, namely Poloxamer 188... ." Applicants further submit that Example 7 of Lee fails to teach or suggest Applicants' invention as claimed in claim 72 for two reasons. First, Example 7 of Lee teaches the use of ethanol as a co-solvent which would fall outside the scope of Applicants' claim 72. Second, Example 7 teaches a total excipient concentration of 18% which exceeds Applicants' "no more than 15%" limitation.

The Office Action further cites to Lee at col. 7, line 32+ in addressing claims 51,52,56 (8% Poloxamer 188) and col. 7, line 65+ in addressing claims 53-54, and 57 (7% Poloxamer 188). With respect to the former, Applicants respectfully submit that, as mentioned previously, Lee's Example 7 at col. 7, line 32 et seq. fails to teach Applicants' invention as claimed because it fails to teach or suggest a formulation whose total excipients falls within Applicants' limitation of no more than 15% excipients. With respect the latter, Applicants respectfully submit that Example 5 at col. 6, line 65 et seq. of Lee is inapplicable because it includes SOLUTOL HS 15, a lipid-based component, that is an example of an excipient that Applicants' aqueous invention as disclosed and claimed is specifically directed to avoiding.

The Office Actions' subsequent citation to Lee at col. 7 lines 16-65 for "PEG 0.5%-5%" to address claims 39-57 raises the same issues, namely that Example 7 is inapposite because it teaches an excipient concentration of 18%, exceeding Applicants' 15% limitation on total excipients. Moreover, Example 7 teaches 5% ethanol and Example 6 teaches 1.5% ethanol while Applicants' independent claim 49, and all claims depending therefrom, explicitly exclude "other alcohol". Likewise, Applicants claims 39-48 and 51-57 explicitly require Poloxamer 188 while Examples 6 and 8 of Lee (also within the Office Action's cited range) teach use of Poloxamer 407. The Office Action then cites again to Example 7 (col. 7, lines 47-50) for sorbitan generally and polyoxyethylene 20 sorbitan specifically for claims 62 and 63, but again, Example 7 teaches use of Poloxamer 407 (in contrast with Applicants' claim 1 and 49 requirement of Poloxamer 188) and teaches use of ethanol (in contrast with Applicants' claim 49 requirement of no other alcohol).

The Office Action continues by citing to May for its purported teaching of benzyl alcohol. May teaches sterile pharmaceutical compositions of propofol as emulsions that include an antimicrobial agent and identifies benzyl alcohol as such an agent. May and its examples are principally directed to lipid-based formulations and rightly so - Applicants indicate in their own disclosure that lipid-based formulations are susceptible to growth for which there is an anti-microbial need. Applicants respectfully submit that May fails to teach or suggest a propofol

formulation that is an aqueous, lipid-free composition having a total excipient concentration below 15% and that is clear to the eye.

The Office Action continues at page 8 by citing to Glen for the general use of citric acid but it fails, however, to specify to which claim it applies its citation. To the extent Applicants understand this rejection, they respectfully traverse it on the basis that their claims are distinguishable from the cited prior art on the grounds discussed above.

In conclusion, with respect to the Office Action's rejection of claims 49-64, 66-68, and 71-74 under § 103(a) based on Glen and Meadow in view of May and Lee, Applicants respectfully submit that the cited prior art fails to teach or suggest each of the limitations of Applicants' invention as claimed and therefore cannot serve as grounds for a proper prima facie case of obviousness. Accordingly, Applicants respectfully request that this rejection be withdrawn.

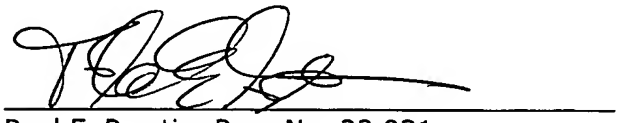
D. Section 103(a) (Glen in view of Meadow and further in view of May and Lee): Claims 75-77.

The Office Action rejection identifies claims 75-77, however, it would appear, that claim 75 was included in error. Applicants infer this conclusion from the context of the rejection's assertions with respect to sodium or potassium hydroxide and hydrochloric acid as Applicants' claimed pH modifiers. Applicants' claim 75 includes no pH modifier limitation. With respect to claims 76 and 77, Applicants respectfully submit that claim 76 depends from claims 1 or 49 and, in the alternative, includes each of their limitations. For the reasons stated above, Applicants believe that claims 1 and 49 are allowable over the cited prior art. Therefore, withdrawal of the rejection of claim 76 is respectfully requested. Likewise, independent claim 77 includes limitations (e.g. "up to 15% excipients," "Poloxamer 188," "clear to the naked eye") that, for the reasons stated above, render Applicants' invention as claimed nonobvious as compared to the cited prior art.

Conclusion:

For the foregoing reasons, Applicants believe that all of pending claims 1, 11,12, 20, 23-37, 39-64, 66-68, 71-78 are in condition for allowance. Early and favorable notification to this effect is respectfully requested.

Respectfully submitted,



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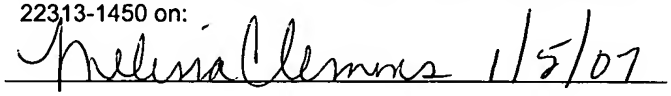

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